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STERNE KESSLER GOLDSTEIN & FOX
1100 NEW YORK AVENUE NW
SUITE 600
WASHINGTON DC 20005-3934

EXAMINER	
NGUYEN, D	

ART UNIT	PAPER NUMBER
1633	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/849,117	Hallenbeck et al.
Examiner	**Group Art Unit**
Dave Nguyen	1633

☒ Responsive to communication(s) filed on *Oct 20, 1998*.

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-3, 7-12, 16-22, 26-33, and 37-44* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-3, 7-12, 16-22, 26-33, and 37-44* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *11*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

The specification has been amended; claims 4-6, 13-15, 23-25, and 34-36 have been canceled, claims 41-44 have been added, and claims 1, 7, 9-11, 16, 19-22, 26-33, and 37-40 have been added by the response filed October 13, 1998.

Claims 1-3, 7-12, 16-22, 26-33, and 37-44 are pending to which the following grounds of rejection remain and/or are applicable.

Claims 9-12, 16-18 as amended remain rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for claims drawn to methods for distributing a polynucleotide in any tissue *in vivo,* particularly in view of the reason set forth at pages 7-9 of the Office action dated April 13, 1998.

In response to applicant' s assertion (the response, pages 27-30) that the nature of the present invention alone would not cause one skilled in the art to reasonably doubt its asserted usefulness in distributing polynucleotides to cells and tissues, that Applicants should not be required to substantiate their presumptively correct disclosure to overcome the present invention under 35 U.S.C. 112, firs paragraph, *e.g., Guidelines for Examination of Applications for Compliance with the Utility Requirement,* that the Guidelines is also applicable to § 112, first paragraph, rejections, *e.g., In re Brana,* and that undue experimentation is not required to carry out the invention on the basis of applicant's disclosure, *e.g., Ex parte Forman,* and *In re Wands,* the comments are not persuasive because the statutory ground of rejection is not for utility under

35 U.S.C. 101 but for lack of enablement under 35 U.S.C. 112 first paragraph. A finding that applicant' s assertions are credible does not necessitate a finding that, based upon the as-filed specification, one skilled in the art would have been able to have practiced what is claimed. The issue at hand is not usefulness *per se*, but rather whether one skilled in the art would have been able to have practiced what is claimed based upon the as-filed specification. In the case of *Brana,* the issue revolved around the functionality of a chemical compound that was structurally similar to that of the prior art. Such is not the case in the claims of the invention under instant consideration. The claims are drawn to methods for distributing any polynucleotide in any tissue *in vivo* wherein the only disclosed use of the *in vivo* distribution to accomplish an unspecified therapeutic effect. Given that the art of record indicating that gene therapy methods remain unpredictable at the time the invention was made, it is not apparent how one skilled in the art practice the gene therapy methods as claimed for treating any disease or disorder in any subject without undue experimentation, on the basis of applicant's disclosure. Thus, based upon the evidence in the record, which demonstrates that there is a reasonable basis for questioning the assertions regarding the enablement of the claimed invention, the present claims are properly rejected under 35 U.S.C. 112, first paragraph, and discussions of *Ex parte Forman, In re Wands* as to "undue experimentation" are not persuasive. Furthermore, while a single embodiment may provide broad enablement in cases involving predictable factors, in cases involving unpredictable factors, *e.g.*, methods for distributing a polynucleotide at any target site *in vivo* have a therapeutic

effect in any subject having any disease, a further showing is required.

In response to applicant' s assertion (the response, pages 30-31) that the cited Crystal, Coghlan, Gunzburg, Mastrangelo, and Ledley references simply indicate that there was no clinical evidence, that there is simply no reason for the over-extension of this opinion, and that the examiner requires data to demonstrate the clinical efficiency of the claimed invention, and that there is no requirement for clinical data to prove that an application is in compliance with 35 U.S.C. § 112, first paragraph, *e.g., Cross v. Iizuka, In re Brana, Bigham v. Godtfredsen, Fiers v. Revel, In re Ziegler, and Fujikawa v. Wattanasin, Ex parte Bhide,* and *Sie v. Herskowitz,* the comments are not persuasive because the instant and prior Office actions did not state a requirement for clinical data. The above argument by applicant does not factually establish a correlation between the factual data obtained from applicants disclosure to the enablement of the claimed invention, given the doubts expressed by the art of record, as set forth in the previous and in this Office action. While *Cross v. Iizuka* is directed to enablement issues under 112, first paragraph regarding "how to use" imidazole derivative compounds which exhibit a pharmacological activity, the claimed invention of this application is directed to methods for distributing a polynucleotide at a target tissue *in vivo* so as to have a therapeutic effect, *e.g.,* treating any pathophysiological state in a human. Thus, it is not apparent how *Cross v. Iizuka* is reasonably correlated to the claimed invention, nor is it apparent the present application claims are directed to a prosthetic device for which applicant relies upon *In re Brana.*

In response to applicant' s assertion (page 32) that the *in vitro* assays described in the present specification would be generally predictive of *in vivo* test results, *e.g., Cross,* and that the presently pending claims are fully enabled by the present invention, the comments are not persuasive in view of the reasons indicated in the preceding paragraphs.

The following is a quotation of the second paragraph of 35 U.S.C. 112, second paragraph:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the application regards as his invention.

Claims 9-12, 16-18 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 9-12, 16-18 remain indefinite in the recitation of the phrase "distributing a polynucleotide in a tissue *in vivo*" because it is not apparent as to what are the metes and bounds of the distribution of a polynucleotide *in vivo* in accomplishing a beneficial effect. Furthermore, claim 17 is indefinite because it is not apparent as to what is the stated effect of *in vivo* gene expression of a heterologous gene in accomplishing a beneficial effect.

In response to applicant' s assertion (the response, page 37) that there is no requirement for a claim to recite a beneficial effect in order to meet the definiteness requirements of 35 U.S.C. § 112, second paragraph, and that one skilled in the art would understand the beneficial effects of

the distribution of a polynucleotide *in vivo,* when viewing the language of claims 9-17 in the context of the specification as originally filed, the comments are not persuasive because the specification does not contained a clear definition of what diseases or disorders being treated by the distribution of a polynucleotide in a tissue *in vivo.*

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-5, 8-14, 17-24, 27-35, and 38-40 as amended are rejected under 35 U.S.C. 103(a) as being unpatentable over Martuza *et al.* (US Pat No. 5,585,096) taken with Roth *et al.* (US Pat No. 5,747,469), Huber *et al.* (IDS, Doc. Ref. AM1), Burton *et al.* (US Pat No.

5,416,017, IDS), Smith *et al.* (Human Gene Therapy, 5:29-35, 1994), Abe *et al.* (PNAS, 90:282-286, 1993, IDS), Grooteclaes *et al.*, Cancer Res., 54:4193-4199, 1994), Kovarik *et al.*, J. Biol. Chem, 268:9917-9926, 1993), and Max-Audit, J. Biol. Chem. 268:5431-5437, 1993).

Martuza *et al.* disclose and a method for killing tumor cells *in vivo* comprising administration of tissue-specific-replication competent herpes simplex virus vectors to tumor cells. The tissue-specific-replication competent herpes simplex virus vectors contain a tissue-specific or cell-specific transcriptional regulatory sequence that is operatively linked to an essential herpes simplex virus gene, wherein said transcription regulatory sequence effects expression of said gene in a specific tissue or cell, such that said virus replicates only in said tissue or cell. Columns 11 and 12 disclosed the tissue-specific-replication competent herpes simplex virus vectors and methods of using the herpes simplex virus vectors to express a heterologous gene for specific killing of tumor cells. Columns 15 and 16 provide the guidance as to how to construct and produce the tissue-specific-replication competent herpes simplex virus vectors. Examples 2-5 provide a detailed description as to how to use the replication-competent viral vectors in *in vivo* extracranial and *in vivo* intracranial tumor killing models. Martuza *et al.* do not teach a gene therapy method for killing tumor cells wherein a replication-conditional adenovirus vector comprising a tumor-specific promoter is employed.

However, at the time the invention was made, Roth *et al.* teach a method for killing tumor cells *in vivo* wherein a recombinant adenovirus encoding a tumor suppressor gene is employed

(abstract, claims 2, 15, 105). Roth *et al.* teach that an adenovirus system has potential advantages for gene delivery *in vivo,* such as ease of producing high titer virus, high infection efficiency, and infectivity of many types of cells (column 2 bridging column 3). Column 7, lines 28-30 specifically disclose that "other than the requirement that the adenovirus vectors be engineered to express p53, the nature of the initial adenovirus is not believed to be crucial to the successful practice of the invention".

Regarding claims drawn to tumor specific promoters, Huber *et al.*, Burton *et al.*, Smith *et al.*, Abe *et al.*, Grooteclaes *et al.*, Kovarik *et al.*, and Max-Audit all teach that tumor specific promoters, and tissue-specific promoters including α-fetoprotein, DF3, tyrosinase, and ErbB2 are known in the art at the time the invention was made.

It would have been obvious for one of ordinary skill in the art to have modified the gene therapy method for killing tumor cells of Martuza *et al.* with a recombinant adenoviral vector expressing a cytotoxic gene, as taught by Roth *et al.*, to enhance the killing of tumor cells *in vitro* and/or *in vivo,* particularly since Roth *et al.* teach that an adenovirus system has potential advantages for gene delivery *in vivo,* such as ease of producing high titer virus, high infection efficiency, and infectivity of many types of cells. One of ordinary skill in the art would have been motivated to practice the claimed invention a reasonable expectation of success, particularly since Martuza *et al.* teach the advantages of employing replication conditional vectors in the killing of tumor cells wherein a tissue specific promoter is employed, and since Roth *et al.* teach that an

adenovirus system has potential advantages for gene delivery *in vivo,* such as ease of producing high titer virus, high infection efficiency, and infectivity of many types of cells (column 2 bridging column 3).

It would also have been obvious for one of ordinary skill in the art to have constructed and employed the tissue-specific-replication competent adenoviral vectors of Martuza *et al.* taken with Roth *et al.* by using a known tumor or tissue-specific promoter operably linked to a viral gene necessary for adenoviral replication for expressing a cytotoxic gene in a tumor cell-specific fashion in order to target and deliver the cytotoxic gene product to tumor cells. One of ordinary skill in the art would have a reasonable expectation of success in constructing and employing the tissue-specific-replication competent adenoviral vectors, particularly since Huber *et al.*, Burton *et al.*, Smith *et al.*, Abe *et al.*, Grooteclaes *et al.*, Kovarik *et al.*, and Max-Audit all teach that tumor specific promoters, and tissue-specific promoters including α-fetoprotein, DF3, tyrosinase, and ErbB2 are known in the art at the time the invention was made and employed for delivery of gene products to targeted cells.

Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made and was as a whole, *prima facie* obvious.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE **THREE MONTHS** FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUORY PERIOD FOR RESPONSE EXPIRE LATER THAN **SIX MONTHS** FROM THE DATE OF THIS FINAL ACTION.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Dave Nguyen* whose telephone number is **(703) 305-2024**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Brian Stanton*, may be reached at **(703) 308-2801**

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 304-0196**.

Dave Nguyen

Bruce Campell

BRUCE R. CAMPELL
PRIMARY EXAMINER
GROUP 1800